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10/633,629	08/05/2003	Ayoub Rashtchian	60126-002US	6375

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EXAMINER	
POPA, ILEANA	
ART UNIT	PAPER NUMBER
1633	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/633,629	RASHTCHIAN ET AL.	
	Examiner	Art Unit	
	ILEANA POPA	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 June 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25-42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/04/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-24 have been cancelled.

Claims 25-42 are pending and under examination.

Response to Arguments

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 25-27, 32-36, 38, and 42 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Li et al. (Brain Research Protocols, 2000, 5: 211-217, of record), in view of both Lopez Garcia et al. (Analyst, 1991, 116: 517-520) and Stemmer et al. (US Patent No. 5,834,252).

Li et al. teach quantification of mRNA expression by TaqMan hot-start real-time RT-PCR, wherein the real-time RT-PCR is carried out in a MicroAmp Optical 96-well reaction plate to detect multiple target nucleic acids, wherein each well contains an aliquot of a master mix comprising Tween 20 and AmpliTaq Gold DNA polymerase (i.e., a thermostable polymerase), and wherein the amplified mRNA is optically detected (claims 25-27, 32-36, 38, and 42) (Abstract; p. 212, column 1, Supply and reagents; p. 213, column 1 bridging column 2 and Fig. 1).

Li et al. do not teach including and anti-foam agent in their master mix (claims 25 and 38). However, doing such is suggested by the prior art. For example, Lopez Garcia et al. teach that the small air bubbles formed in the presence of detergents worsen the reproducibility of quantification by optical detection; Lopez Garcia et al. teach using anti-foam agents to overcome this problem (p. 518, column 1). Stemmer et al. teach that anti-foam agents could be used in PCR (i.e., the anti-foam agents do not substantially inhibit the polymerase) (column 10, lines 7-30). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Li et al. by further including an anti-foam agent in their master mix to achieve the predictable result of improving the reproducibility (i.e., accuracy) of optical detection in RT-PCR. Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Applicant argues that, in citing Stemmer et al. and Lopez Garcia, the Examiner picks and chooses from the disclosures only so much as to support her obviousness rejection. This type of "cherry picking" is improper as the Federal Circuit has stated:

> [i]t is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one skilled in the art. (Bausch & Lomb, Inc., v. Barnes- Hind/Hydrocurve, Inc., 796, F.2d 443, 448 (Fed. Cir. 1986) (quoting in re Wesslau, 355 F. 2d 238, 241 (CCPA 1965)).

Nothing in Stemmer teaches or describes quantitative PCR, as recited in the instant claims. Moreover, Stemmer must be considered for all that it teaches, not merely any part of the reference that supports the Examiner's assertions regarding obviousness. In particular, as previously described in the Berninger declaration,

Stemmer suggests use of conditions that are incompatible with either PCR or quantitative PCR. One of ordinary skill in the art reading Stemmer clearly would recognize this incompatibility and would not be motivated by any alleged teachings regarding PCR.

Similarly, nothing in the Lopez Garcia reference can be said to describe an issue with small bubbles formed in the presence of detergents worsening the reproducibility of quantification by optical detection, when the entirety of the reference is considered. That reference states:

> When surfactant concentration was higher than about 0.2%, the slurries gave rise to abundant foam and small air bubbles were trapped in the sample loop of the FI manifold, making reproducibility worse.

Applicants respectfully submit that the FI manifold, which is described in the Experimental section on page 517 of Lopez Garcia, is upstream of the optical path. Put more simply, Lopez Garcia appears to be discussing, for want of a better term an "air lock" or partial "air lock" in the tube that feeds the nebulizer of the atomic absorption instrument. Applicants respectfully submit that bubbles at that point in the sample path simply are not present in the optical path. Even if air bubbles passed through the nebulizer they would be destroyed in the high temperatures present in the flame of the instrument prior to reaching the optical path. In sum, the optical path passes through gas phase materials (e.g., the flame and/or its effluent), not liquids where air bubbles could exist. In view of the foregoing, Applicants respectfully submit that after a complete reading, a skilled artisan would understand that Lopez Garcia does not teach, and indeed cannot be cited for teaching that air bubbles interfere with optical detection

due to their presence in an instrument's optical path, or that antifoam agents affect that problem.

Lopez Garcia, which is directed to atomic absorbance spectroscopic techniques, cannot be considered analogous art capable of being combined with references directed to PCR. Atomic absorbance spectroscopy as applied in that reference requires the destructive testing liquid sample by drawing them into a flame, which precludes the repeated sample analysis over multiple cycles that is necessary for real time PCR. The reference deals with the analysis of metal particle slurries and the difficulties of foaming in those samples, not in compositions used for potymerase chain reaction. Moreover, nothing in Lopez Garcia teaches or fairly suggests that nucleic acids, or for that matter any other non-metal containing organic molecule, can be quantitated by atomic absorption spectrometry as such molecules would be burned in the process. For at least the foregoing reasons, Lopez Garcia cannot be said to be analogous art, or event to stand for the proposition relied upon by the Examiner in formulating the rejection. Further to the foregoing, Applicants submit that at the time of their invention, it would have been considered inconsistent with the art-recognized stabilizing effect of detergents on purified polymerase enzymes to employ a polymerase in an assay/reaction mixture containing an antifoam agent as antifoam agents interact with detergents and can render them unavailable to stabilize the polymerase. This is evidenced by the teachings of U.S. Patents 6,127,155 and 6,242,235, and EP1970440A 1, submitted herewith and that will be discussed in a declaration by Dr. Michael Smith that will be submitted hereafter.

In view of the preceding remarks, Applicants respectfully submit that a *prima facie* case of obviousness has not been established as the Lopez Garcia and Stemmer references fail to remedy the admitted deficiencies of the Li et al. Moreover, the references as set forth above do not provide a motivation for their combination, particularly as the Lopez Garcia reference does not teach problems with bubbles present during optical detection as alleged by the Examiner.

In the event that the Examiner seeks to maintain that a *prima facie* case of obviousness exists despite the manifold deficiencies of the cited reference, Applicants submit that any evidence of obviousness is rebutted by the surprising results described in Applicants' specification. Specifically, Applicants' specification shows that the instantly claimed methods surprisingly allow detection measurements that are free of artifacts. For example, FIGS 2 and 4 of the instant specification illustrate the deleterious effect of foaming on threshold cycle (Ct) determination in real-time PCR from identical reactions containing 20 copies of template DNA per reaction. The only difference between the two reactions is the inclusion of antifoam in the reactions recorded in FIG 4. FIG 2 shows that fluorescence readings were distorted with respect to baseline and Ct determinations in qPCR reactions without the addition of anti-foaming agents. Specifically, the bubble error in wells H1 to H6 resulted in Ct values ranging from 33 to 38, which represents approximately a 15 fold difference. FIG 4, however, surprisingly shows that the addition of anti-foam not only limited bubble formation, but produced a stable baseline allowing for a more accurate reading. The

greatest variation in these antifoam containing tests was 1 Ct, which represent approximately a 2 fold difference in quantification.

In summary, Applicants submit that the Examiner has failed to present a *prima facie* case of obviousness. Moreover, even if, for the sake of argument only, it is assumed that a *prima facie* case of obviousness exists, the evidence of surprising results as described above negates such *prima facie* case. Accordingly, Applicants request the withdrawal of the rejection.

Applicant's arguments are acknowledged; however, the rejection is maintained for the following reasons:

Applicant argues that nothing in Stemmer teaches or describes quantitative PCR, as recited in the instant claims. In response to Applicant's arguments against the reference individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Stemmer does not have to teach each and every claim limitation. If he did, this would have been anticipation and not an obviousness-type rejection.

The argument that Stemmer suggests conditions incompatible with either PCR or quantitative PCR is not new and was previously addressed. Furthermore, the prior art teaches using antifoaming agents in nucleic acid amplification reactions (see Durmowicz et al., U.S. Patent No. 5,962,273, of record). While Durmowicz et al. teach SDA and not PCR, one of skill in the art would recognize that if the presence of an

antifoam agent in a SDA reaction is successful then the presence of an antifoam agent in PCR , as taught by Stemmer, would have a reasonable expectation of success as well. Based on the teachings in the art as a whole, one of skill in the art would have known that antifoam agents could be used in nucleic acid amplification reactions (including PCR) and would have been motivated to use such in order to improve PCR accuracy.

Applicant argues that, when the entirety of the reference is considered, nothing in Lopez Garcia describes an issue with small bubbles worsening the reproducibility of quantification by optical detection. This argument is not found persuasive. Lopez Garcia clearly teaches that antifoams improve reproducibility of the results (i.e., optical detection). Therefore, it is clear that the presence of bubbles interferes with optical detection. The fact that the FI manifold is upstream of the optical path does not change this. Elimination of air bubbles before feeding the sample into the nebulizer ensures continuous loading of sample into the nebulizer (and therefore, the optical path of the detection device), which results in improved accuracy. By reading Lopez Garcia, one of skill in the art would readily understand that air bubbles interfere with optical detection and would have been motivated to eliminate the air bubbles before feeding the samples into the detection device such that the air bubbles would not interfere with the optical detection and quantification by PCR. One of skill in the art would have known to achieve this by including antifoam agents in the reaction buffer.

Applicant argues that Lopez Garcia is not analogous art. In response to this argument, it has been held that a prior art reference must either be in the field of

applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a basis for rejection of the claimed invention. See *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). In this case, since Lopez Garcia is concerned with improving the accuracy of optical detection by using antifoam agents, the reference is reasonably pertinent to the particular problem with which the applicant was concerned (i.e., improving the accuracy of optical detection in PCR by using antifoam agents). For these reasons, the argument is not found persuasive.

Applicant's argument that antifoam agents interact with detergents and can render them unavailable to stabilize the polymerase is just an argument not supported by any evidence. U.S. Patents 6,127,155 and 6,242,235, and EP1970440A 1 do not provide any evidence to this extent. These references teach PCR in the presence of detergents and do not mention antifoam agents at all. Therefore, these references do not proved evidence that antifoam agents render detergents unavailable. The art as a whole does not provide such evidence. For these reasons, the argument is not found persuasive.

Applicant's arguments of unexpected results (i.e., is not found persuasive because the prior art teaches that addition of antifoam agents results in accurate reading.

For the reasons set forth above, Applicant's arguments are not found persuasive and the rejection is maintained.

4. Claims 25-28, 32-38, and 42 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Li et al. taken with both Lopez Garcia et al. and Stemmer et al., in further view of Blaschke et al. (J Immunol Methods, 2000, 246: 79-90).

The teachings of Li et al., Lopez Garcia et al., and Stemmer et al. are applied as above for claims 25-27, 32-36, 38, and 42. Li et al., Lopez Garcia et al., and Stemmer et al. teach using TaqMan probes and not a fluorescent nucleic acid-binding dye (claims 28 and 37). Blaschke et al. teach that real-time RT-PCR can be performed by using either TaqMan probes or nucleic acid-binding dyes (p. 80, column 2, first paragraph, p. 82, column 1, second paragraph). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Li et al., Lopez Garcia et al., and Stemmer et al. by replacing their TaqMan probe with a nucleic acid-binding dye to achieve the predictable result of quantifying the RT-PCR products. Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Applicant traversed the instant rejection on the grounds that Blaschke et al. do not cure the deficiencies noted above. Applicant's argument is acknowledged; however, the rejection is maintained for the reasons set forth above.

5. Claims 25-27, 29-36, and 38-42 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Li et al. taken with both Lopez Garcia et al. and Stemmer et al., in further view of each Kyle (US Patent No. 5,658,767), Sigma catalog (1998) and Wierenga (US Patent No. 5,968,889).

The teachings of Li et al., Lopez Garcia et al., and Stemmer et al. are applied as above for claims 25-27, 32-36, 38, and 42. Li et al., Lopez Garcia et al., and Stemmer et al. do not specifically teach using 520-US as an anti-foam agent (claims 30 and 40). Kyle et al. teach the 1520-US as a suitable silicone-based anti-foaming agent (column 11, Example 3). It would have been obvious to one of skill in the art, at the time the invention was made, to use the method of Stemmer et al. with 1520-US as an anti-foam agent to achieve the predictable result of improving the reproducibility (i.e., accuracy) of optical detection in RT-PCR.

Li et al., Lopez Garcia et al., Stemmer et al., and Kyle do not teach using two anti-foam agents (claims 29, 31, 39, and 41). However, doing such is suggested by the prior art. For example, the Sigma catalog teaches that anti-foaming agents can be supplied as a mixture of organic anti-foams and silicone-based anti-foams, and that O-30 is an organic antifoaming agent. Wierenga teaches that silicone-based anti-foaming agents are not that effective, and that the addition of organic anti-foamers results in a synergistic anti-foaming combination (Abstract, column 1, lines 38-51, and also column bridging column 2). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Li et al., Lopez Garcia et al., Stemmer et al., and Kyle by further adding an organic anti-foamer such as O-30, with a reasonable expectation of success. The motivation to do so is provided by Wierenga who teaches that the addition of organic anti-foamers to silicone-based anti-foamers results in a synergistic anti-foaming combination. One of skill in the art would have had a reasonable expectation of success in using such a combination because Sigma catalog

describes such combinations and because the art teaches that such combinations are very efficient in controlling foam formation. Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Applicant traversed the instant rejection on the grounds that none of the secondary references cures the deficiencies noted above. Applicant's argument is acknowledged; however, the rejection is maintained for the reasons set forth above.

Conclusion

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILEANA POPA whose telephone number is (571)272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ileana Popa/
Primary Examiner, Art Unit 1633